CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074833

Trade Name : ACYCLOVIR 200MG CAPSULES

Generic Name: Acyclovir 200mg Capsules

Sponsor : Aesgen, Inc.

Approval Date: April 22, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074833

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074833

APPROVAL LETTER

ANDA 74-833

APR 22 1997

Aesgen, Inc.
Attention: Robert B. Brownfield, Ph.D.
5051 New Centre Drive
Suite 103
Wilmington, NC 28403

Dear Dr. Brownfield:

This is in reference to your abbreviated new drug application dated January 4, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Acyclovir Capsules, 200 mg.

Reference is also made to your amendments dated May 29, 1996, August 30, 1996, January 30, 1997, and March 14, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Acyclovir Capsules, 200 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Zovirax® Capsules, 200 mg of Glaxo Wellcome Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours

4/22/97

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074833

FINAL PRINTED LABELING

Each capsule contains 200 mg acyclovir, USP.
USUAL DOSAGE: See package circular for full prescribing information.
Dispense in a tight, light-resistant container, as defined in the USP.
Store between 15° and 25° C (59° and 77° F). Protect from light and moisture.

Manufactured for:
Aesgen Inc
Wilmington, NC 28403
By:
MOVA PHARMACEUTICAL CORPORATION
Caguas, P.R. 00725, USA

4

ACYCLOVIR Capsules

NDC 55370-542-09

200 mg

CAUTION: Federal law prohibits dispensing without prescription.

1000 Capsules

LOT #:

EXP. DATE:

APPROVED

6234300MV

ISSUED 08/96

Each capsule contains 200 mg acyclovir, USP.
USUAL DOSAGE: See package circular for full prescribing information.
Dispense in a tight, light-resistant container, as defined in the USP.
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Caguas, P.R. 00725, USA

4

ACYCLOVIR Capsules

NDC 55370-542-07

200 mg

CAUTION: Federal law prohibits dispensing without prescription.

100 Capsules

LOT #:

EXP. DATE:

6234200MV

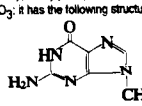
ISSUED 08/96

ACYCLOVIR CAPSULES

DESCRIPTION

Acyclovir is an antiviral drug. Acyclovir capsules are formulated for oral administration. Each capsule of acyclovir contains 200 mg of acyclovir and the inactive ingredients corn starch, lactose monohydrate, magnesium stearate, and sodium lauryl sulfate. The capsule shell consists of gelatin, FD&C Blue No. 2, and titanium dioxide. Printed with FD&C Blue No. 2 Aluminum Lake, and Iron Oxides.

The chemical name of acyclovir is 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]-6*H*-purin-6-one; it has a molecular formula of $C_8H_{11}N_5O_3$; it has the following structural formula:



Acyclovir is a white to off-white, crystalline powder with a molecular weight of 225.21, and a maximum solubility in water of 2.5 mg/mL at 37°C.

CLINICAL PHARMACOLOGY

Mechanism of Antiviral Effects: Acyclovir is a synthetic purine nucleoside analogue with *in vitro* and *in vivo* inhibitory activity against human herpes viruses including herpes simplex types 1 (HSV-1) and 2 (HSV-2); varicella-zoster virus (VZV), Epstein-Barr virus (EBV), and cytomegalovirus (CMV). In cell culture, acyclovir has the highest antiviral activity against HSV-1, followed in decreasing order of potency against HSV-2, VZV, EBV, and CMV.[1]

The inhibitory activity of acyclovir for HSV-1, HSV-2, VZV, and EBV is highly selective. The enzyme thymidine kinase (TK) of normal uninfected cells does not effectively use acyclovir as a substrate. However, TK encoded by HSV, VZV, and EBV[2] converts acyclovir into acyclovir monophosphate, a nucleotide analogue. The monophosphate is further converted into diphosphate by cellular guanylate kinase and into triphosphate by a number of cellular enzymes.[3] Acyclovir triphosphate interferes with herpes simplex virus DNA polymerase and inhibits viral DNA replication. Acyclovir triphosphate also inhibits cellular α-DNA polymerase, but to a lesser degree. *In vitro*, acyclovir triphosphate can be incorporated into growing chains of DNA by viral DNA polymerase and to a much smaller extent by cellular α-DNA polymerase.[4] When incorporation occurs, the DNA chain is terminated.[5,6] Acyclovir is preferentially taken up and selectively converted to the active triphosphate form by herpesvirus-infected cells. Thus, acyclovir is much less toxic *in vitro* for normal uninfected cells because: 1) less is taken up; 2) less is converted to the active form; 3) cellular α-DNA polymerase is less sensitive to the effects of the active form. The mode of acyclovir phosphorylation in cytomegalovirus-infected cells is not clearly established, but may involve virally induced cell kinases or an unidentified viral enzyme. Acyclovir is not efficiently activated in cytomegalovirus-infected cells, which may account for the reduced susceptibility of cytomegalovirus to acyclovir *in vitro*.

Microbiology: The quantitative relationship between the *in vitro* susceptibility of herpes simplex and varicella-zoster viruses to acyclovir and the clinical response to therapy has not been established in humans, and virus sensitivity testing has not been standardized. Sensitivity testing results, expressed as the concentration of drug required to inhibit by 50% the growth of virus in cell culture (ID_{50}), vary greatly depending upon the particular assay used,[7] the cell type employed,[8] and the laboratory performing the test.[1] The ID_{50} of acyclovir against HSV-1 isolates may range from 0.02 mcg/mL (plaque reduction in Vero cells) to 5.9 to 13.5 mcg/mL (plaque reduction in green monkey kidney [GMK] cells).[1] The ID_{50} against HSV-2 ranges from 0.01 mcg/mL to 9.9 mcg/mL (plaque reduction in Vero and GMK cells, respectively).[1]

Using a dye-uptake method in Vero cells,[9] which gives ID_{50} values approximately 5- to 10-fold higher than plaque reduction assays, 1417 HSV isolates (553 HSV-1 and 864 HSV-2) from approximately 500 patients were examined over a 5-year period.[10] These assays found that 90% of HSV-1 isolates were sensitive to ≤ 0.9 mcg/mL acyclovir and 50% of all isolates were sensitive to ≤ 0.2 mcg/mL acyclovir. For HSV-2 isolates, 90% were sensitive to ≤ 2.2 mcg/mL and 50% of all isolates were sensitive to ≤ 0.7 mcg/mL of acyclovir. Isolates with significantly diminished sensitivity were found in 44 patients. It must be emphasized that neither the patients nor the isolates were randomly selected and, therefore, do not represent the general population. Most of the less sensitive HSV clinical isolates have been relatively deficient in the viral TK.[11-19] Strains with alterations in viral TK[20] or viral DNA polymerase[21] have also been reported. Prolonged exposure to low concentrations (0.1 mcg/mL) of acyclovir in cell culture has resulted in the emergence of a variety of acyclovir-resistant strains.[22]

The ID_{50} against VZV ranges from 0.17 to 1.53 mcg/mL (yield reduction, human foreskin fibroblasts) to 1.85 to 3.98 mcg/mL (foci reduction, human embryo fibroblasts [HEF]). Reproduction of EBV genome is suppressed by 50% in superinfected Raji cells or P3HR-1 lymphoblastoid cells by 1.5 mcg/mL acyclovir. CMV is relatively resistant to acyclovir with ID_{50} values ranging from 2.3 to 17.6 mcg/mL (plaque reduction, HEF cells) to 1.82 to 56.8 mcg/mL (DNA hybridization, HEF cells). The latent state of the genome of any of the human herpesviruses is not known to be sensitive to acyclovir.[1]

Pharmacokinetics: The pharmacokinetics of acyclovir after oral administration have been evaluated in 6 clinical studies involving 110 adult patients. In one uncontrolled study of 35 immunocompromised patients with herpes simplex or varicella-zoster infection, acyclovir capsules were administered in doses of 200 to 1000 mg every 4 hours, 6 times daily for 5 days, and steady-state plasma levels were reached by the second day of dosing. Mean steady-state peak and trough concentrations following the final 200 mg dose were 0.49 mcg/mL (0.47 to 0.54 mcg/mL) and 0.31 mcg/mL (0.18 to 0.41 mcg/mL), respectively, and following the final 800 mg dose were 2.8 mcg/mL (2.3 to 3.1 mcg/mL) and 1.8 mcg/mL (1.3 to 2.5 mcg/mL), respectively. In another uncontrolled study of 20 younger immunocompetent patients with recurrent genital herpes simplex infections, acyclovir capsules were administered in doses of 800 mg every 6 hours, 4 times daily for 5 days; the mean steady-state peak and trough concentrations were 1.4 mcg/mL (0.66 to 1.8 mcg/mL) and 0.55 mcg/mL (0.14 to 1.1 mcg/mL), respectively.

In general, the pharmacokinetics of acyclovir in children is similar to adults. Mean half-life after oral doses of 300 mg/m^2 and 600 mg/m^2, in children ages 7 months to 7 years, was 2.6 hours (range 1.59 to 3.74 hours).

In a multiple-dose crossover study where 23 volunteers received acyclovir as one 200 mg capsule, one 400 mg tablet, and one 800 mg tablet 6 times daily,

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In a multiple-dose crossover study where 23 volunteers received acyclovir as one 200 mg capsule, one 400 mg tablet, and one 800 mg tablet 6 times daily, absorption decreased with increasing dose and the estimated bioavailabilities of acyclovir were 20%, 15%, and 10%, respectively. The decrease in bioavailability is believed to be a function of the dose and not the dosage form. It was demonstrated that acyclovir is not dose proportional over the dosing range 200 mg to 800 mg. In this study, steady-state peak and trough concentrations of acyclovir were 0.83 and 0.46 mcg/mL, 1.21 and 0.63 mcg/mL, and 1.61 and 0.83 mcg/mL for the 200, 400, and 800 mg dosage regimens, respectively.

In another study, the influence of food on the absorption of acyclovir was not apparent.

Following oral administration, the mean plasma half-life of acyclovir in volunteers and patients with normal renal function ranged from 2.5 to 3.3 hours. The mean renal excretion of unchanged drug accounts for 14.4% (8.6% to 19.8%) of the orally administered dose. The only urinary metabolite (identified by high performance liquid chromatography) is 9-[(carboxymethoxy) methyl] guanine. The half-life and total body clearance of acyclovir are dependent on renal function. A dosage adjustment is recommended for patients with reduced renal function (see **DOSAGE AND ADMINISTRATION**).

Orally administered acyclovir in children less than 2 years of age has not yet been fully studied.

INDICATIONS AND USAGE

Acyclovir capsules are indicated for the treatment of initial episodes and the management of recurrent episodes of genital herpes in certain patients.

Acyclovir capsules are indicated for the acute treatment of herpes zoster (shingles) and chickenpox (varicella).

Genital Herpes Infections:

The severity of disease is variable depending upon the immune status of the patient, the frequency and duration of episodes, and the degree of cutaneous or systemic involvement. These factors should determine patient management, which may include symptomatic support and counseling only, or the institution of specific therapy. The physical, emotional, and psychosocial difficulties posed by herpes infections as well as the degree of debilitation, particularly in immunocompromised patients, are unique for each patient, and the physician should determine therapeutic alternatives based on his or her understanding of the individual patient's needs. Thus, orally administered acyclovir is not appropriate in treating all genital herpes infections. The following guidelines may be useful in weighing the benefit/risk considerations in specific disease categories:

First Episodes (primary and nonprimary infections-commonly known as initial genital herpes):

Double-blind, placebo-controlled studies[23,24,25] have demonstrated that orally administered acyclovir significantly reduced the duration of acute infection (detection of virus in lesions by tissue culture) and lesion healing. The duration of pain and new lesion formation was decreased in some patient groups. The promptness of initiation of therapy and/or the patient's prior exposure to herpes simplex virus may influence the degree of benefit from therapy. Patients with mild disease may derive less benefit than those with more severe episodes. In patients with extremely severe episodes, in which prostration, central nervous system involvement, urinary retention, or inability to take oral medication require hospitalization and more aggressive management, therapy may be best initiated with intravenous acyclovir.

Recurrent Episodes: Double-blind, placebo-controlled studies[16,26-32] in patients with frequent recurrences (6 or more episodes per year) have shown that orally administered acyclovir given daily for 4 months to 3 years prevented or reduced the frequency and/or severity of recurrences in greater than 95% of patients.

In a study of 283 patients who received acyclovir 400 mg (two 200 mg capsules) twice daily for 3 years, 45%, 52%, and 63% of patients remained free of recurrences in the first, second, and third years, respectively. Serial analyses of the 3-month recurrence rates for the 283 patients showed that 71% to 87% were recurrence-free in each quarter, indicating that the effects are consistent over time.

The frequency and severity of episodes of untreated genital herpes may change over time. After 1 year of therapy, the frequency and severity of the patient's genital herpes infection should be re-evaluated to assess the need for continuation of therapy with acyclovir. Re-evaluation will usually require a trial off acyclovir to assess the need for reinstitution of suppressive therapy. Some patients, such as those with very frequent or severe episodes before treatment, may warrant uninterrupted suppression for more than a year.

Chronic suppressive therapy is most appropriate when, in the judgement of the physician, the benefits of such a regimen outweigh known or potential adverse effects. In general, orally administered acyclovir should not be used for the suppression of recurrent disease in mildly affected patients. Unanswered questions concerning the relevance to humans of *in vitro* mutagenicity studies and reproductive toxicity studies in animals given high parenteral doses of acyclovir for short periods (see **PRECAUTIONS: Carcinogenesis, Mutagenesis, Impairment of Fertility**) should be borne in mind when designing long-term management for individual patients. Discussion of these issues with patients will provide them the opportunity to weigh the potential for toxicity against the severity of their disease. Thus, this regimen should be considered only for appropriate patients with annual re-evaluation.

Limited studies[31,32] have shown that there are certain patients for whom intermittent short-term treatment of recurrent episodes is effective. This approach may be more appropriate than a suppressive regimen in patients with infrequent recurrences.

Immunocompromised patients with recurrent herpes infections can be treated with either intermittent or chronic suppressive therapy. Clinically significant resistance, although rare, is more likely to be seen with prolonged or repeated therapy in severely immunocompromised patients with active lesions.

Herpes Zoster Infections: In a double-blind, placebo-controlled study of 187 normal patients with localized cutaneous zoster infection (93 randomized to acyclovir and 94 to placebo), acyclovir (800 mg 5 times daily for 10 days) shortened the times to lesion scabbing, healing, and complete cessation of pain, and reduced the duration of viral shedding and the duration of new lesion formation.[33]

In a similar double-blind, placebo-controlled study in 83 normal patients with herpes zoster (40 randomized to acyclovir and 43 to placebo), acyclovir (800 mg 5 times daily for 7 days) shortened the times to complete lesion scabbing, healing, and cessation of pain, reduced the duration of new lesion formation, and reduced the prevalence of localized zoster-associated neurologic symptoms (paresthesia, dysesthesia, or hyperesthesia).[34]

Chickenpox: In a double-blind, placebo-controlled efficacy study in 110 normal patients, ages 5 to 16 years, who presented **within 24 hours** of the onset of a typical chickenpox rash, acyclovir was administered orally 4 times daily for 5 to 7 days at doses of 10, 15, or 20 mg/kg depending on the age group. Treatment with acyclovir reduced the maximum number of lesions (336 vs. greater than 500; lesions beyond 500 were not counted). Treatment with acyclovir also shortened the mean time to 50% healing (7.1 days vs. 8.7

patients with fever (temperature [illegible]
by the second day of treatment, and decreased the mean number of residual lesions on Day 28.[36,37] There were no substantial differences in VZV-specific humoral or cellular immune responses measured at 1 month following treatment in patients receiving acyclovir compared to patients receiving placebo.[38]

Diagnosis: Diagnosis is confirmed by virus isolation. Accelerated viral culture assays or immunocytology allow more rapid diagnosis than standard viral culture. For patients with initial episodes of genital herpes, appropriate examinations should be performed to rule out other sexually transmitted diseases. While cutaneous lesions associated with herpes simplex and varicella-zoster infections are often characteristic, the finding of multinucleated giant cells in smears prepared from lesion exudate or scrapings may provide additional support to the clinical diagnosis.[39] Multinucleated giant cells in smears do not distinguish varicella-zoster from herpes simplex infections.

CONTRAINDICATIONS

Acyclovir capsules are contraindicated for patients who develop hypersensitivity or intolerance to the components of the formulation.

WARNINGS

Acyclovir capsules are intended for oral ingestion only.

PRECAUTIONS

General: Acyclovir has caused decreased spermatogenesis at high parenteral doses in some animals and mutagenesis in some acute studies at high concentrations of drug (see **PRECAUTIONS: Carcinogenesis, Mutagenesis, Impairment of Fertility**). The recommended dosage should not be exceeded (see **DOSAGE AND ADMINISTRATION**).

Exposure of herpes simplex and varicella-zoster isolates to acyclovir *in vitro* can lead to the emergence of less sensitive viruses. The possibility of the appearance of less sensitive viruses in humans must be borne in mind when treating patients. The relationship between the *in vitro* sensitivity of herpes simplex or varicella-zoster virus to acyclovir and clinical response to therapy has yet to be established (see **CLINICAL PHARMACOLOGY: Microbiology**).

Because of the possibility that less sensitive virus may be selected in patients who are receiving acyclovir, all patients should be advised to take particular care to avoid potential transmission of virus if active lesions are present while they are on therapy. In severely immunocompromised patients, the physician should be aware that prolonged or repeated courses of acyclovir may result in selection of resistant viruses which may not fully respond to continued acyclovir therapy.

Caution should be exercised when administering acyclovir to patients receiving potentially nephrotoxic agents since this may increase the risk of renal dysfunction.

Information for Patients: Patients are instructed to consult with their physician if they experience severe or troublesome adverse reactions, they become pregnant or intend to become pregnant, they intend to breastfeed while taking orally administered acyclovir, or they have any other questions.

Genital Herpes Infections: Genital herpes is a sexually transmitted disease and patients should avoid intercourse when visible lesions are present because of the risk of infecting intimate partners. Acyclovir capsules are for oral ingestion only. Medication should not be shared with others. The prescribed dosage should not be exceeded. Acyclovir does not eliminate latent viruses. Patients are instructed to consult with their physician if they do not receive sufficient relief in the frequency and severity of their genital herpes recurrences.

There are still unanswered questions concerning reproductive/gonadal toxicity and mutagenesis; long-term studies are continuing. Decreased sperm production has been seen at high doses in some animals; a placebo-controlled clinical study using 400 mg or 1000 mg of acyclovir per day for 6 months in humans did not show similar findings.[40] Chromosomal breaks were seen *in vitro* after brief exposure to high concentrations. Some other currently marketed medications also cause chromosomal breaks, and the significance of this finding is unknown. A placebo-controlled clinical study using 800 mg of acyclovir per day for 1 year in humans did not show any abnormalities in structure or number of chromosomes.[28]

Herpes Zoster Infections: Adults age 50 or older tend to have more severe shingles, and treatment with acyclovir showed more significant benefit for older patients. Treatment was begun within 72 hours of rash onset in these studies, and was more useful if started within the first 48 hours.

Chickenpox: Although chickenpox in otherwise healthy children is usually a self-limited disease of mild to moderate severity, adolescents and adults tend to have more severe disease. Treatment was initiated within 24 hours of the typical chickenpox rash in the controlled studies, and there is no information regarding the effects of treatment begun later in the disease course. It is unknown whether the treatment of chickenpox in childhood has any effect on long-term immunity. However, there is no evidence to indicate that treatment of chickenpox with acyclovir would have any effect on either decreasing or increasing the incidence or severity of subsequent recurrences of herpes zoster (shingles) later in life. Intravenous acyclovir is indicated for the treatment of varicella-zoster infections in immunocompromised patients.

Drug Interactions: Co-administration of probenecid with intravenous acyclovir has been shown to increase the mean half-life and the area under the concentration-time curve. Urinary excretion and renal clearance were correspondingly reduced.[41] The clinical effects of this combination have not been studied.

Carcinogenesis, Mutagenesis, Impairment of Fertility: The data presented below include references to peak steady-state plasma acyclovir concentrations observed in humans treated with 800 mg given orally 5 times a day (dosing appropriate for treatment of herpes zoster) or 200 mg given orally 5 times a day (dosing appropriate for treatment of genital herpes). Plasma drug concentrations in animal studies are expressed as multiples of human exposure to acyclovir at the higher and lower dosing schedules (see **CLINICAL PHARMACOLOGY: Pharmacokinetics**).

Acyclovir was tested in lifetime bioassays in rats and mice at single daily

doses of up to 450 mg/kg administered by gavage. There was no statistically significant difference in the incidence of tumors between treated and control animals, nor did acyclovir shorten the latency of tumors. At 450 mg/kg/day, plasma concentrations were 3 to 6 times human levels in the mouse bioassay and 1 to 2 times human levels in the rat bioassay.

Acyclovir was tested in two *in vitro* cell transformation assays. Positive results were observed at the highest concentration tested (31 to 63 times human levels) in one system and the resulting morphologically transformed cells formed tumors when inoculated into immunosuppressed, syngeneic, weanling mice. Acyclovir was negative (40 to 80 times human levels) in the other, possibly less sensitive, transformation assay.

In acute cytogenetic studies, there was an increase, though not statistically significant, in the incidence of chromosomal damage at maximum tolerated parenteral doses of acyclovir (100 mg/kg) in rats (62 to 125 times human levels) but not in Chinese hamsters; higher doses of 500 and 1000 mg/kg were clastogenic in Chinese hamsters (380 to 760 times human levels). In addition, no activity was found after 5 days dosing in a dominant lethal study in mice (36 to 73 times human levels). In all 4 microbial assays, no evidence of mutagenicity was observed. Positive results were obtained in 2 of 7 genetic toxicity assays using mammalian cells *in vitro*. In human lymphocytes, a positive response for chromosomal damage was seen at concentrations 150 to 300 times the acyclovir plasma levels achieved in humans. At one locus in mouse lymphoma cells, mutagenicity was observed at concentrations 250 to 500 times human plasma levels. Results in the other five mammalian cell loci follow: at 3 loci in a Chinese hamster ovary cell line, the results were inconclusive at concentrations at least 1850 times human levels; at 2 other loci in mouse lymphoma cells, no evidence of mutagenicity was observed at concentrations at least 1500 times human levels.

Acyclovir has not been shown to impair fertility or reproduction in mice (450 mg/kg/day, p.o.) or in rats (25 mg/kg/day, s.c.). In the mouse study, plasma levels were 9 to 18 times human levels, while in the rat study they were 8 to 15 times human levels. At a higher dose in the rat (50 mg/kg/day, s.c.), there was a statistically significant increase in postimplantation loss, but no concomitant decrease in litter size. In female rabbits treated subcutaneously with acyclovir subsequent to mating, there was a statistically significant decrease in implantation efficiency but no concomitant decrease in litter size at a dose of 50 mg/kg/day (16 to 31 times human levels). No effect upon implantation efficiency was observed when the same dose was administered intravenously (53 to 106 times human levels). In a rat peri- and postnatal study at 50 mg/kg/day s.c. (11 to 22 times human levels), there was a statistically significant decrease in the group mean numbers of corpora lutea, total implantation sites, and live fetuses in the F1 generation. Although not statistically significant, there was also a dose-related decrease in group mean numbers of live fetuses and implantation sites at 12.5 mg/kg/day and 25 mg/kg/day, s.c. The intravenous administration of 100 mg/kg/day, a dose known to cause obstructive nephropathy in rabbits, caused a significant increase in fetal resorptions and a corresponding decrease in litter size (plasma levels were not measured). However, at a maximum tolerated intravenous dose of 50 mg/kg/day in rabbits (53 to 106 times human levels), no drug-related reproductive effects were observed.

Intraperitoneal doses of 80 or 320 mg/kg/day acyclovir given to rats for 6 and 1 months, respectively, caused testicular atrophy. Plasma levels were not measured in the 1-month study and were 24 to 48 times human levels in the 6-month study. Testicular atrophy was persistent through the 4-week postdose recovery phase after 320 mg/kg/day; some evidence of recovery of sperm production was evident 30 days postdose. Intravenous doses of 100 and 200 mg/kg/day acyclovir given to dogs for 31 days caused aspermatogenesis. At 100 mg/kg/day plasma levels were 47 to 94 times human levels, while at 200 mg/kg/day they were 159 to 317 times human levels. No testicular abnormalities were seen in dogs given 50 mg/kg/day I.V. for 1 month (21 to 41 times human levels) and in dogs given 60 mg/kg/day orally for 1 year (6 to 12 times human levels).

Pregnancy: Teratogenic Effects: Pregnancy Category C. Acyclovir was not teratogenic in the mouse (450 mg/kg/day, p.o.), rabbit (50 mg/kg/day, s.c. and I.v.), or in standard tests in the rat (50 mg/kg/day, s.c.). These exposures resulted in plasma levels 9 and 18, 16 and 106, and 11 and 22 times, respectively, human levels. In a non-standard test in rats, there were fetal abnormalities, such as head and tail anomalies, and maternal toxicity.[42] In this test, rats were given 3 s.c. doses of 100 mg/kg acyclovir on gestation day 10, resulting in plasma levels 63 and 125 times human levels. There are no adequate and well-controlled studies in pregnant women.

Acyclovir should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus. Although acyclovir was not teratogenic in standard animal studies, the drug's potential for causing chromosome breaks at high concentration should be taken into consideration in making this determination.

Nursing Mothers: Acyclovir concentrations have been documented in breast milk in two women following oral administration of acyclovir and ranged from 0.6 to 4.1 times corresponding plasma levels.[43,44] These concentrations would potentially expose the nursing infant to a dose of acyclovir up to 0.3 mg/kg/day. Caution should be exercised when acyclovir is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in pediatric patients less than 2 years of age have not been adequately studied.

ADVERSE REACTIONS

Herpes Simplex: Short-Term Administration: The most frequent adverse events reported during clinical trials of treatment of genital herpes with orally administered acyclovir were nausea and/or vomiting in 8 of 298 patient treatments (2.7%) and headache in 2 of 298 (0.6%). Nausea and/or vomiting occurred in 2 of 287 (0.7%) patients who received placebo.

Less frequent adverse events, each of which occurred in 1 of 298 patient treatments with orally administered acyclovir (0.3%), included diarrhea, dizziness, anorexia, fatigue, edema, skin rash, leg pain, inguinal adenopathy, medication taste, and sore throat.

Long-Term Administration: The most frequent adverse events reported in a clinical trial for the prevention of recurrences with continuous administration of 400 mg (two 200 mg capsules) 2 times daily for 1 year in 586 patients treated with acyclovir were: nausea (4.8%), diarrhea (2.4%), headache (1.9%), and rash (1.7%). The 589 control patients receiving intermittent treatment of recurrences with acyclovir for 1 year reported diarrhea (2.7%), nausea (2.4%), headache (2.2%), and rash (1.5%).

The most frequent adverse events reported during the second year by 390 patients who elected to continue daily administration of 400 mg (two 200 mg capsules) 2 times daily for 2 years were headache (1.5%), rash (1.3%), and paresthesia (0.8%). Adverse events reported by 329 patients during the third year included asthenia (1.2%), paresthesia (1.2%), and headache (0.9%).

Herpes Zoster: The most frequent adverse events reported during three clinical trials of treatment of herpes zoster (shingles) with 800 mg of oral acyclovir 5 times daily for 7 to 10 days in 323 patients were: malaise (11.5%), nausea (8.0%), headache (5.9%), vomiting (2.5%), diarrhea (1.5%), and constipation (0.9%). The 323 placebo recipients reported malaise (11.1%), nausea (11.5%), headache (11.1%), vomiting (2.5%), diarrhea (0.3%), and constipation (2.4%).

Chickenpox: The most frequent adverse events reported during three clinical trials of treatment of chickenpox with oral acyclovir in 495 patients were: diarrhea (3.2%), abdominal pain (0.6%), rash (0.6%), vomiting (0.6%), and flatulence (0.4%). The 498 patients receiving placebo reported: diarrhea (2.2%), flatulence (0.8%), and insomnia (0.4%).

Observed During Clinical Practice: Based on clinical practice experience in patients treated with oral acyclovir in the U.S., spontaneously reported adverse events are uncommon. Data are insufficient to support an

Chickenpox: The most frequent adverse events reported during three clinical trials of treatment of chickenpox with oral acyclovir in 495 patients were: diarrhea (3.2%), abdominal pain (0.6%), rash (0.6%), vomiting (0.6%) and flatulence (0.4%). The 498 patients receiving placebo reported: diarrhea (2.2%), flatulence (0.8%), and insomnia (0.4%).

Observed During Clinical Practice: Based on clinical practice experience in patients treated with oral acyclovir in the U.S., spontaneously reported adverse events are uncommon. Data are insufficient to support an estimate of their incidence or to establish causation. These events may also occur as part of the underlying disease process. Voluntary reports of adverse events which have been received since market introduction include:

General: fever, headache, pain, peripheral edema, and rarely, anaphylaxis

Nervous: confusion, dizziness, hallucinations, paresthesia, seizure, somnolence (These symptoms may be marked, particularly in older adults.)

Digestive: diarrhea, elevated liver function tests, gastrointestinal distress, nausea

Hemic and Lymphatic: leukopenia, lymphadenopathy

Musculoskeletal: myalgia

Skin: alopecia, pruritus, rash, urticaria

Special Senses: visual abnormalities

Urogenital: elevated creatinine

OVERDOSAGE

Patients have ingested intentional overdoses of up to 100 capsules (20 g) of acyclovir, with no unexpected adverse effects.

Precipitation of acyclovir in renal tubules may occur when the solubility (2.5 mg/mL) in the intratubular fluid is exceeded. Renal lesions considered to be related to obstruction of renal tubules by precipitated drug crystals occurred in the following species: rats treated with i.v. and i.p. doses of 20 mg/kg/day for 21 and 31 days, respectively, and at s.c. doses of 100 mg/kg/day for 10 days; rabbits at s.c. and i.v. doses of 50 mg/kg/day for 13 days; and dogs at i.v. doses of 100 mg/kg/day for 31 days. A 6-hour hemodialysis results in a 60% decrease in plasma acyclovir concentration. Data concerning peritoneal dialysis are incomplete but indicate that this method may be significantly less efficient in removing acyclovir from the blood. In the event of acute renal failure and anuria, the patient may benefit from hemodialysis until renal function is restored (see **DOSAGE AND ADMINISTRATION**).

DOSAGE AND ADMINISTRATION

Treatment of Initial Genital Herpes: 200 mg (one 200 mg capsule) every 4 hours, 5 times daily for 10 days.

Chronic Suppressive Therapy for Recurrent Disease: 400 mg (two 200 mg capsules) 2 times daily for up to 12 months, followed by re-evaluation. See **INDICATIONS AND USAGE** and **PRECAUTIONS** for considerations on continuation of suppressive therapy beyond 12 months. Alternative regimens have included doses ranging from 200 mg 3 times daily to 200 mg 5 times daily.

Intermittent Therapy: 200 mg (one 200 mg capsule) every 4 hours, 5 times daily for 5 days. Therapy should be initiated at the earliest sign or symptom (prodrome) of recurrence.

Acute Treatment of Herpes Zoster: 800 mg (four 200 mg capsules) every 4 hours orally, 5 times daily for 7 to 10 days.

Treatment of Chickenpox: *Children (2 years of age and older):* 20 mg/kg **per dose** orally four times daily (80 mg/kg/day) for 5 days. Children over 40 kg should receive the adult dose for chickenpox.

Adults and children over 40 kg: 800 mg four times daily for 5 days. Therapy should be initiated at the earliest sign or symptom of chickenpox to derive the maximal benefits of therapy.

Patients With Acute or Chronic Renal Impairment: Comprehensive pharmacokinetic studies have been completed following intravenous acyclovir infusions in patients with renal impairment. Based on these studies, dosage adjustments are recommended in the following chart for genital herpes and herpes zoster indications:

Normal Dosage Regimen	Creatinine Clearance (mL/min/1.73m^2)	Adjusted Dosage Regimen	
		Dose (mg)	Dosing Interval
200 mg every 4 hours	>10	200	every 4 hours, 5x daily
	0-10	200	every 12 hours
400 mg every 12 hours	>10	400	every 12 hours
	0-10	200	every 12 hours
800 mg every 4 hours	>25	800	every 4 hours, 5x daily
	10-25	800	every 8 hours
	0-10	800	every 12 hours

Hemodialysis: For patients who require hemodialysis, the mean plasma half-life of acyclovir during hemodialysis is approximately 5 hours. This results in a 60% decrease in plasma concentrations following a 6-hour dialysis period. Therefore, the patient's dosing schedule should be adjusted so that an additional dose is administered after each dialysis.[45,46]

Peritoneal Dialysis: No supplemental dose appears to be necessary after adjustment of the dosing interval.[47,48]

HOW SUPPLIED

Acyclovir capsules (blue, opaque cap and body) containing 200 mg acyclovir and printed in black with 200 and A05 on opposite sides of the body - Bottles of 100 (NDC 55370-542-07), and bottles of 1000 (NDC 55370-542-09). Store between 15° and 25°C (59° and 77°F). Protect from light and moisture.

CAUTION: Federal law prohibits dispensing without prescription.

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Manufactured by:
MOVA PHARMACEUTICAL CORPORATION
Caguas, Puerto Rico 00725, USA
Issued 02/97

Item # 633800MV

For:
Aesgen Inc
Wilmington, NC 28403

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074833

CHEMISTRY REVIEW(S)

ANDA APPROVAL SUMMARY

ANDA: 74-833 DRUG PRODUCT: Acyclovir

FIRM: Aesgen, Inc. DOSAGE FORM: Capsule STRENGTH: 200 mg

CGMP STATEMENT/EIR UPDATE STATUS: Acceptable for all on 5/3/96.

BIO STUDY: The single-dose bioequivalence fasting study, single-dose bioequivalence non-fasting study and dissolution testing conducted on 200 mg capsules (Lot #95063A) were acceptable by the Division of Bioequivalence on 12/17/96.

VALIDATION -(DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):

Active Ingredient: N/A, product is compendial refer to memo dated 11/14/90 regarding Compliance Program Guidance Manual # 7346.832, code 52832 for ANDAs and AADAs.

Finish Dosage Form: Sent to Southeast Regional Laboratory on 11/19/96. Acceptable for regulatoy purposes on 3/17/97.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?:

Protocol: Satisfactory

Exp.Date: 24 months - 40°C, 75% R.H. and R.T. (25°C, 60%R.H.), 3 months, each container/closure system, 1 lot. Lot #95063A/#MLC2731 (AAI/Mova) ⇒ 100's, Lot #BP00144/#MCL2732 (AAI/Mova) ⇒ 1000's. All made from Lot #MLC273V (Mova).

Container/Closure systems are the same.

LABELING: Container: Satisfactory for 100's and 1000's.
Insert: Satisfactory in FPL.

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?):
units (, Lot #MLC273V), source of NDS acceptable .

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA THE SAME PROCESS?):
units Lot #MLC273V).

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?:
units , process the same.

CHEMIST: Norman Gregory 4/24/97 DATE: 4/17/97

SUPERVISOR: Glen Smith 4/21/97 DATE: 4/17/97

1. CHEMISTRY REVIEW NO. 3

2. ANDA #74-833

3. NAME AND ADDRESS OF APPLICANT

Aesgen, Inc.
5051 New Centre Drive
Wilmington, NC 28403

4. LEGAL BASIS FOR SUBMISSION
The applicant certifies , that to the best of it knowledge, U.S. Patent No. 4,199,574 will expire on April 22, 1997 and is not covered by any exclusivity. Will not market product before April 22, 1997.

Innovator: Burroughs Wellcome - Zovirax®

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME
Acyclovir

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Firm:
1/4/96 - Original.
5/29/96 - O/NC, Bio.
8/30/96 - Response to Bio. def. letter.
10/25/96 - Response to 1st def. letter (chem. & labeling).
12/19/96 - Response to Labeling def. phone memo-fax dated 11/13/96.
1/30/97 - Response to 2nd def. letter (chem.). Subject of this review.
3/14/97 - Response to phone memo, labeling.

FDA:
2/20/96 - Acknowledgment.
7/9/96 - Bio. def. letter.
7/31/96 - 1st def. letter (chem. & labeling).
9/16/96 - Meeting minutes with AAI.
11/13/96 - Phone memo, Labeling faxed their deficiencies to firm.
12/17/97 - Bio. review acceptable.
12/20/96 - 2nd def. letter (chem.).
12/23/96 - Bio. letter, no further questions.
2/11/97 - Phone memo, Labeling faxed their deficiencies to firm.

10. PHARMACOLOGICAL CATEGORY
Antiviral

11. Rx or OTC
℞

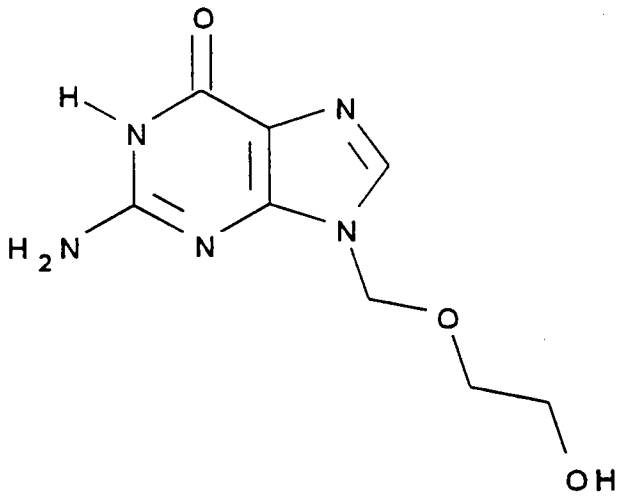
12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Capsule

14. POTENCY
200 mg

15. CHEMICAL NAME AND STRUCTURE

Acyclovir USP
$C_8H_{11}N_5O_3$; M.W. = 225.21



9-[(2-Hydroxyethoxy)methyl]guanine. CAS [59277-89-3]

16. RECORDS AND REPORTS
N/A

17. COMMENTS
DMF's, Bio., labeling, methods validation and EER satisfactory.

18. CONCLUSIONS AND RECOMMENDATIONS
Approval

19. REVIEWER:
Norman Gregory

DATE COMPLETED:
2/14/97 (TA never sent, change to AP)
4/17/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074833

BIOEQUIVALENCE REVIEW(S)

FC

ANDA 74-833

Aesgen, Inc.
Attention: Robert B. Brownfield, Ph.D.
5051 New Centre Drive
Wilmington NC 28403

DEC 23 1998

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Acyclovir Capsules 200 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The following dissolution testing will need to be incorporated into your stability and quality control programs:

   The dissolution testing should be conducted as per **FDA** recommended method in 900 mL of deaerated water at 37°C using USP 23 apparatus 1 (basket) at 100 RPM. The test drug should meet the following specifications:

   Not less than (Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

Rabindra Patnaik, Ph.D.
Acting Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

DEC 17 1996

Acyclovir 200 mg capsules
ANDA 74-833
Reviewer: A.P.Patel
File: x:\apatel\74833a.896

Aesgen, Inc.
Wilmimgton, NC
Submission date:
Aug. 30, 1996

REVIEW OF AMENDMENT

Background

The firm has submitted an amendment in response to the deficiencies for ANDA#74-833, Acyclovir 200 mg capsules.

***Deficiencies* and Responses:**

1.

All standards and controls were prepared using human plasma. The error noted was an oversight from a template used for a non-related study.

2.

The firm has carried out data analysis as requested.

Summary of Pharmacokinetic Data:

Fasting Study: **90% C.I.Limits of Ln-transformed parameters:**

LS Means	AUC_{0-t}	$AUC_{0-\infty}$	Cmax
Test	7.647	7.724	6.185
Reference	7.651	7.728	6.212
90% C.I.	0.895 - 1.109	0.900 - 1.103	0.878 - 1.079

Non-Fasting Study: **Ln-Transformed Pharmacokinetics Data**

LS Means	AUC_{0-t}	$AUC_{0-\infty}$	C_{max}
Test-Fast	7.58	7.67	6.23
Test+ food	7.56	7.65	6.11
Ref+ food	7.55	7.65	6.11
(Test+ food)/(Ref+ food)	1.00	1.00	1.00
(Test+ food)/(Test+Fast)	0.997	0.997	0.981

The test/reference ratios for pharmacokinetic parameters under non-fasting conditions are close to unity and satisfy FDA requirements.

3. *Please provide actual bio-batch yield.*

   Total # of capsules manufactured

4. *Upper limit of linearity, presumably mis-typed, on page 308 and 1143, please verify error.*

   Error has been corrected.

5. *Stability of drug, data provided for a maximum of 7 days only at various temperatures and 4 freeze-thaw cycles. Firm has claimed stability of standards and QC samples for up to 1 year at -20°C. Please provide stability data for 1 year and, if available, 3 or 6 month data.*

   Firm has supplied 1 year stability data. Data for 3 and 6 month availability not addressed. control should have read based on original submission (typographical error).

6. *Instruction for preparation of standard (vol. 2 of 7, page 314, item 2d) is incorrect. Present instruction will result in standard instead of standard (a typographical error).*

   Error has been corrected.

7. *The firm provided dissolution data for the test and the reference 200 mg Acyclovir capsules using their method:*

   Apparatus: USP, Apparatus II (paddles), at 50 RPM
   Medium: water, 900 mL @ 37°C

Samples: *10 mL @ 15, 30, 45, 60, and 75 minutes*
Quantitation:
Specifications: *NLT (Q), dissolved in 45 minutes.*

Please provide dissolution data using FDA-recommended method:

Medium: 900 mL water
Apparatus 1 (basket) at 100 RPM
Quantitation method should be stated
Tolerances: NLT (Q) in 30 minutes

The firm has pointed out in this amendment that they had originally supplied dissolution data table and graph which did not correspond to the same lot of Acyclovir capsules. They have now supplied the correct dissolution data from the bio-batch.

Medium: 900 mL water
Apparatus 1 (basket) at 100 RPM
Quantitation method
Tolerances: NLT (Q) in 30 minutes

Mean (%CV), N=12	**15 min.**	**30 min.**	**45 min.**	**60 min.**	**∞** (75 min)
200 mg cap, test	93.3 (10.6)	100.0 (1.4)	99.9 (1.3)	99.8 (1.1)	100.1 (1.0)
200 mg Zovirax[R], ref.	77.8 (5.9)	91.5 (4.9)	98.4 (2.1)	99.3 (2.0)	98.6 (2.5)

Recommendation:

1. A single-dose bioequivalence fasting study conducted by Aesgen Inc., on its Acyclovir 200 mg capsules, lot#95063A(AAI)/MLC2731(MOVA) comparing it to Zovrax[R] 200 mg capsules, lot #5M1287, manufactured by Burroughs-Wellcome, is acceptable to the Division of Bioequivalence. The study demonstrates that Aesgen's Acyclovir 200 mg capsule is deemed bioequivalent to the reference product, Zovrax[R] 200 mg capsule, manufactured by Burroughs-Wellcome.

2. A single-dose bioequivalence non-fasting study conducted by Aesgen Inc., on its Acyclovir 200 mg capsules, lot#95063A(AAI)/MLC2731(MOVA) comparing it to Zovrax[R] 200 mg capsules, lot #5M1287, manufactured by Burroughs-Wellcome, is acceptable to the Division of Bioequivalence. The study demonstrates that Aesgen's Acyclovir 200 mg capsule is deemed bioequivalent to the reference product, Zovrax[R] 200 mg capsule, manufactured by Burroughs-Wellcome.

3. The dissolution testing conducted by Aesgen Inc., on its Acyclovir 200 mg capsules (lot#95063A), is acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted as per FDA recommended method in 900 mL of deaerated water at 37°C using USP 23 apparatus 1 (basket)

The firm should be informed of the recommendations.

12/6/96

A.P.Patel
Division of Bioequivalence
Review Branch III

RD INITIALED RMHATRE
FT INITIALED RMHATRE Date: 12/6/96
Ramakant M. Mhatre, Ph.D.
Chief, Branch III
Division of Bioequivalence

Concur: Date: 12/17/96

Rabindra Patnaik, Ph.D.
Acting Director
Division of Bioequivalence

cc: ANDA# 74-833 (Original, Duplicate), HFD-658 (A.P.Patel), Drug File, Division File.

ANDA 74-833

JUL 9 1996

Aesgen, Inc.
Attention: Robert B. Brownfield, Ph.D.
5051 New Centre Drive
Wilmington, NC 28403

Dear Sir:

Reference is made to the bioequivalence data submitted in your Abbreviated New Drug Application January 4, 1996, for Acyclovir Capsules, 200 mg. The Office acknowledges the receipt of an amendment dated May 29, 1996, which will be reviewed according to Office policy.

The Office of Generic Drugs has reviewed the bioequivalence data submitted on January 4, 1996, and the following comments are provided for your consideration:

1.

2.

3. Please provide actual yield of the bio-batch.

4. The upper limit of linearity is presumably mis-typed, as instead of on page 308 and 1143; please clarify.

5. Stability of drug: The data submitted only provided stability data for a maximum of 7 days at various temperatures and 4 freeze-thaw cycles. In the submission you have specified the stability of standards and QC samples is up to 1 year at -20°C. Please provide stability data for 1 year and, if available, 3 or 6 month data.

6. Instruction for preparation of standard (vol. 2 of 7, page 314, item 2d) is incorrect. Present instruction will result in standard instead of standard; please clarify.

7. Dissolution data were provided for the test and the reference 200 mg acyclovir capsules using the following methodology:

Apparatus:	USP, Apparatus II (paddles), at 50 RPM
Medium:	water, 900 mL @ 37°C
Samples:	10 mL @ 15, 30, 45, 60, and 75 minutes
Quantitation:	
Specifications:	NLT (Q), dissolved in 45 minutes.

Please provide dissolution data using the following FDA-recommended method:

Medium: 900 mL water
Apparatus 1 (basket) at 100 RPM
Quantitation method should be stated
Tolerances: NLT (Q) in 30 minutes

As described under 21 CFR 314.96 an action which will amend this application is required. The amendment will be required to address all of the comments presented in this letter. Should you have any questions, please call Jason A. Gross, Pharm.D., at (301) 594-2290. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

/s/

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation
and Research

JUN 27 1996

Acyclovir 200 mg capsules
ANDA 74-833
Reviewer: A.P.Patel
File: x:\apatel\74833.sd.196

Aesgen, Inc.
Wilmimgton, NC
Submission date:
Jan. 4, 1996

REVIEW OF TWO BIOEQUIVALENCE STUDIES AND DISSOLUTION DATA

Background

Acyclovir, an antiviral agent, is used for the treatment of herpes simplex, varicella zoster virus, Epstein-Barr virus and cytomegalo virus. At the present time, the drug is manufactured and marketed by Burroughs-Wellcome (innovator) in **capsule** dosage form (200 mg), **tablet** (400 mg and 800 mg) and **oral suspension** (200 mg/5 ml) under the trade name Zovirax^{R}.
Upon oral administration, in normal volunteers and in patients with normal renal function, the absorption is slow, variable and incomplete. Peak plasma concentration is reached in 1.5 to 2. hours post drug administration. The elimination is biphasic with the beta phase half-life about 2 to 3 hours. The drug is excreted mainly by the kidney, and about 45% to 79% of the dose is recovered unchanged in the urine. There is one (1) urinary metabolite, 9-carboxymethoxymethyl guanine (CMMG) which is inactive and accounts for 8 -14% of the dose.

A protocol # 95-072 for in-vivo bioequivalency from (submitted on June 5, 1995) was reviewed and approved by the agency for Mova Pharmaceutical (sponsor). Aesgen, Inc. (sponsor) has submitted a study of bioequivalence conducted by in January 1996. The studies compared 200 mg Capsules manufactured by MOVA Pharmaceutical Corp and Burroughs-Wellcome under fasting and non-fasting conditions.

Protocol: IRB#404-95: Two way single dose fasting study of acyclovir 200 mg capsules in normal healthy adult volunteers.

Protocol: IRB#627-95: Three way single dose food effect study of acyclovir 200 mg capsules in normal healthy adult volunteers.

REVIEW OF THE FASTING STUDY:

1. A two-way, single dose, cross-over, fasting bioequivalence study of acyclovir 200 mg capsules in thirty (30) normal healthy adult (20 males and 10 females) volunteers under fasting condition. Subjects age ranged from 18-45 years, and are within 15% of their ideal weight as specified in the protocol. All subjects were selected based on the absence of any clinically significant findings following medical history, physical examination and clinical laboratory evaluations. Inclusion and exclusion criteria in the protocol were followed in the selection of the subjects. The study was completed by twenty seven (27) subjects (19 males and 8 females) with a mean age of 29.15 years. The subjects consisted of twenty six (26)

Caucasians and one native American. Data from drop-outs (subjects #7, 8 and 24) has not been used in the analysis of pharmacokinetics parameters.

2. Study design:
Randomized, single-dose, two-way crossover study under fasting conditions.

3. Study sites:
Clinical and Analytical Study centers

4. Study dates: 7/29/95 - 8/27/95

5. Principal Investigator:

Co-Investigators:

6. Drug administration:
Treatment A (Test): One Aesgen Inc. acyclovir 200 mg capsule (manufactured by MOVA Pharmaceutical Corp.), AAI batch#: 95063A, potency of 100% (n=10), %RSD=1.2, lot size: heoretical) capsules, expiration date: 1/11/96.

Treatment B (Reference): One Burroughs Wellcome's ZOVIRAX^{R} 200 mg capsules, lot #: 5M1287, potency of 97.8%, expiration date: March, 1998.

Each treatment will be given with 240 ml of water following an overnight (10 hour) fast, and washout between treatment is one week.

7. Confinement:
During the confinement periods of this study, the subjects were housed and non-fasting at the clinical facility.

8. Food and fluid intake: Standard lunch and dinner were served on each day of drug administration. The drug products were administered with 240 mL of water. Water was allowed ad lib. after 4 hours post-dose.

9. Sampling schedule:
Blood samples (10 ml/sample) were collected at pre-dose (0 hr), and at 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, and 24 hours post-dose. After centrifugation, plasma was collected and frozen at -70°C until assay.

10. Analytical methodology:
De-proteinated plasma samples were analyzed for acyclovir

RESULTS:

a. Analytical Methodology:

IMPORTANT NOTE: *DO NOT RELEASE THIS SECTION UNDER FOI.*

b. Pharmacokinetics:

Twenty seven (27) subjects completed the study out of thirty (30) initially enrolled in the study. Subjects 7, 8, and 24 discontinued prematurely. Least Squares Means plasma concentrations by sampling time are shown in table 2.

Table 2: (Taken from Table 4, pp165, part 2 of 7 of submission)

LEAST SQUARES MEANS

Sample Time (h)	Test (T)	Reference (R)	Significance*	T/R
Pre-Dose	0.00	0.00	-	
0.25	7.68	5.33	None	1.44
0.50	132.58	74.75	None	1.77
0.75	257.92	186.63	None	1.38
1.00	355.03	272.84	None	1.30
1.33	400.03	341.92	None	1.17
1.67	397.67	393.18	None	1.01
2.00	402.82	415.21	None	0.97
2.50	396.16	412.15	None	0.96
3.00	364.53	393.30	None	0.93
4.00	302.59	319.82	None	0.95
6.00	158.31	164.50	None	0.96
8.00	89.59	94.96	None	0.94
10.00	49.93	52.65	None	0.95
12.00	22.97	21.71	None	1.06
16.00	8.28	8.69	None	0.95
24.00	1.29	2.14	None	0.60

Summary of Pharmacokinetic Data:

Parameter (N=27)	**Trt A (test)** (1x200mg)	**Trt B (Ref)** (1x200mg)	**Ratio of means** (Test/Ref.)
AUC_{0-t}(LSMeans±S.D.)	2283.16±88.99	2296.41±88.99	0.99
$AUC_{0-\infty}$(LSMeans±S.D.)	2392.01±90.30	2411.03±90.30	0.99
Cmax(LSMeans±S.D.)	516.25±20.45	522.32±20.45	0.99
Tmax(LSMeans±S.D.)	1.82±0.15	2.07±0.15	0.88

90% C.I.Limits of Ln-transformed parameters:

	AUC_{0-t}	$AUC_{0-\infty}$	Cmax
Test (LSMeans±S.D.)	7.677±0.041	6.185±0.042	7.723±0.04
Ref (LSMeans±S.D.)	7.676±0.041	6.212±0.042	7.731±0.04
90% C.I.	0.905 - 1.106	0.900 - 1.095	0.878 - 1.079

90%C.I. are within the Agency's requirements for bioequivalence requirements of between 80% - 125%, fasting study is acceptable.

REVIEW OF THE NON-FASTING STUDY:

1. A three-way, single dose, cross-over, bioequivalence food effect study of Aesgen's acyclovir 200 mg capsules (fasting and non-fasting) versus Burroughs-Wellcome's ZOVIRAX^R 200 mg capsules (non-fasting), in twenty four (24) normal healthy adult volunteers.

   Protocol, IRB#627-95, study dates 8/24/95 - 10/1/95.

   This study was conducted in compliance with IRB and informed consent regulations. Subject population consisted of 6 females and 18 males, ages 21-43. The mean age of all subjects was 30.04. Subject 23 withdrew from the study. The mean age of subjects completing the study was 29.48. All subjects met the inclusion/exclusion requirements of the study protocol.

2. **Study site** and Investigators are those described above for fasting study.

3. **Drug administration:**

   Treatment A- (Test, Fasting):

   One Aesgen's acyclovir 200 mg capsule as above, administered after an overnight fast.

   Treatment A+ (Test, Non-Fasting):

   One Aesgen's acyclovir 200 mg capsule, lot #: 95063A(AAI)/MLC2731(MOVA), potency of 100% (n=10), lot size (theoretical) , expiration date: 1/11/1996, administered after a standard high fat breakfast.

   Treatment B (Reference, Non-Fasting):

   One Burroughs-Wellcome's ZOVIRAX^R 200 mg capsule, lot #: 5M1287, potency of 97.8%, expiration date:March1998, administered after a standard high fat breakfast. Each treatment was given with 240 ml of water, and washout between treatment was one week. For treatments A+ and B, high fat breakfast was served after an overnight fast. Breakfast was to be eaten completely (within 30 minutes) prior to drug administration. High fat breakfast consisted of the following items: 1 buttered English Muffin, 1 fried egg, 1 slice American cheese, 1 slice Canadian bacon, 1 serving of hash brown potatoes, 240 ml whole milk and 180 ml orange juice.

4. **Sampling schedule:**

Blood samples (10 ml/sample) were collected at pre-dose (0 hr), and at 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, and 24 hours post-dose. After centrifugation, plasma collected and frozen at -70°C until assay.

5. **Analytical methodology:**

Results:

Analytical Methodology: Since the same method was used in the fasting study, any comment pertaining to the fasting study is applicable to this study.

Pharmacokinetics: 24 subjects began the study, and 23 completed it. Subject 23 withdrew from the study early for events unrelated to the study; therefore this subject's data was not included in the analysis. Mean (Least Squares Means) plasma concentration-time profile of subjects in the study is shown in table 3.

Table 3.

Time (hrs)	A- (Test fast) (1x200mg)	A+(Test + food)	B (Ref + food) (1x200mg)	A+/B (1x200mg)	A+/A-
0.00	0.00	0.00	0.00	–	–
0.25	3.993	0.008	-0.068	0.117	0.002
0.50	122.668	1.962	13.525	0.145	0.016
0.75	277.414	9.191	35.181	0.261	0.033
1.00	389.952	22.239	65.259	0.341	0.057
1.33	434.230	65.723	124.767	0.527	0.151
1.67	449.270	143.716	189.036	0.760	0.319
2.00	425.112	237.491	254.860	0.931	0.559
2.33	395.888	297.637	307.409	0.968	0.752
2.67	369.304	319.930	324.074	0.987	0.866
3.00	341.907	360.720	340.409	1.059	1.055
3.50	315.162	377.257	357.786	1.054	1.197
4.00	266.636	375.119	334.157	1.122	1.407
5.00	202.710	289.680	261.926	1.106	1.429
6.00	149.063	207.146	196.041	1.057	1.389
8.00	80.148	106.402	103.680	1.026	1.328
10.00	41.556	53.753	55.409	0.970	1.294
12.00	22.619	31.213	24.657	1.266	1.379
16.00	4.987	10.093	11.813	0.854	2.023
24.00	0.617	3.340	6.681	0.499	5.413
Mean	214.66	145.63	150.33		
S.D.	169.53	145.82	135.08		
S.E.M.	37.91	32.61	30.20		

Tukey test on plasma acyclovir concentrations, means and S.D. of A-, A+ and B treatments were found not to be significantly different for, between all columns, A- vs A+, A- vs B or

A+ vs B. The data show no significant food effect on absorption of acyclovir in these subjects. However, there appears to be differential absorption of the drug between fasting and non-fasting subjects during earlier time points (time points 0.5h to 2.33h). The plasma drug levels being higher in fasting subjects compared to non-fasting subjects . Post 2.33h, drug levels in fasting subjects begins to decline whereas those in the non-fasting subjects increases to a peak and then declines.

Summary of Pharmacokinetic Data:

Ln-Transformed Pharmacokinetics Data (LSMeans±S.D.)

	AUC_{0-t}	$AUC_{0-\infty}$	C_{max}
Test-Fast	7.61±0.04	7.65±0.04	6.23±0.05
Test+ food	7.59±0.04	7.63±0.04	6.11±0.05
Ref+ food	7.59±0.04	7.65±0.04	6.11±0.05
(Test+ food)/(Ref+ food)	1.00	0.997	1.00
(Test+ food)/(Test-Fast)	0.997	0.997	0.981

The test/reference ratios for pharmacokinetic parameters under non-fasting conditions are close to unity and satisfy FDA requirements.

FORMULATION:

	CAPSULE FILL
Ingredient	**amount per capsule (in mg)**
Acyclovir	200
Lactose,Monohydrate, NF	
Corn Starch, NF	
Sodium lauryl sulfate, NF	
Magnesium stearate, NF	
Purified water, USP	
Size 1 Coni-Snap Blue/Blue Capsule	-----
Total weight (fill+shell):	400 mg

*Purified water removed during drying process

REVIEW OF THE DISSOLUTION STUDY:

Dissolution testing was conducted using the following method and conditions (firm's method):

Apparatus:	USP, Apparatus II (paddles), at 50 RPM
Medium:	water, 900 ml @ 37°C
Samples:	10 mL @ 15, 30, 45, 60, and 75 minutes
Quantitation:	

Specifications: NLT (Q), dissolved in 45 minutes.

Results:

Mean (%RSD), N=12	**15 min.**	**30 min.**	**45 min.**	**60 min.**	***75 min.**
200 mg cap, test	54.6 (15.9)	76.8 (11.3)	83.7 (8.41)	88.2 (6.27)	99.3 (0.8)
200 mg Zovirax^R, ref.	45.0 (17.5)	59.5(15.4)	67.4 (13.3)	73.5 (13.1)	99.3 (2.0)

* Rotational speed of paddles after 60 min time point was increased from 50 RPM to 250 RPM.

Comments:

1.

2.

3. Acyclovir absorption, in the presence of food in these subjects, was not significantly affected.

4. The test/reference ratios for pharmacokinetic parameters under non-fasting conditions are close to unity and satisfy FDA requirements.

5. Upper limit of linearity, presumably mis-typed, as instead of on page 308 and 1143. Firm needs to verify error.

6. Stability of drug, data provided for a maximum of 7 days only at various temperatures and 4 freeze-thaw cycles. Firm has claimed stability of standards and QC samples for upto 1 year at -20^{0}C. Firm should provide, if available, data for 1 yr stability and any shorter times such as 3 or 6 months.

7. Instruction for preparation of standard (vol. 2 of 7, page 314, item 2d) is incorrect. Present instruction will result in standard instead of standard. The firm should confirm the procedure.

8. **Adverse reactions:**

a. Fasting study:

Seven (7) adverse events were reported during the study by 6 subjects. Severity of events were mild and required no medication. One subject (#8) experienced a moderate vaso-vagal reaction after the initial dosing, and discontinued the study.

b. Non-Fasting study:

Four adverse events were reported during this study. Three were mild and one was moderate. All were resolved and none resulted in the subject withdrawing from the study.

Deficiencies:

1.

2.

3. Please provide actual bio-batch yield .

4. Upper limit of linearity, presumably mis-typed, as instead of on page 308 and 1143, please verify error.

5. Stability of drug, data provided for a maximum of 7 days only at various temperatures and 4 freeze-thaw cycles. Firm has claimed stability of standards and QC samples for upto 1 year at -20°C. Please provide stability data for 1 year and, if available, 3 or 6 month data.

6. Instruction for preparation of standard (vol. 2 of 7, page 314, item 2d) is incorrect. Present instruction will result in standard instead of standard (a typographical error).

7. The firm provided dissolution data for the test and the reference 200 mg acyclovir capsules using their method:

Apparatus:	USP, Apparatus II (paddles), at 50 RPM
Medium:	water, 900 ml @ 37°C
Samples:	10 mL @ 15, 30, 45, 60, and 75 minutes
Quantitation:	
Specifications:	NLT Q), dissolved in 45 minutes.

Please provide dissolution data using FDA-recommended method:

Medium: 900 mL water
Apparatus 1 (basket) at 100 RPM
Quantitation method should be stated
Tolerances: NLT (Q) in 30 minutes

Recommendation:

The bioequivalence studies conducted by Aesgen, Inc. on its acyclovir 200 mg capsules, lot#95063A(AAI)/MLC2731(MOVA), comparing it to Burroughs - Wellcome's ZOVIRAX^{R} 200 mg capsules, lot #5M1287 have been found incomplete by the Division of Bioequivalence due to Deficiencies listed.

Deficiencies and Recommendation should be conveyed to the firm.

6/25/96

A.P.Patel
Division of Bioequivalence
Review Branch III

RD INITIALED RMHATRE
FT INITIALED RMHATRE
Ramakant M. Mhatre, Ph.D.
Chief, Branch III
Division of Bioequivalence

Date: 6/25/96

Concur:

Date: 6/27/96

Kieth Chan, Ph.D.
Director
Division of Bioequivalence

cc: ANDA# 74-833 (Original, Duplicate), HFD 630 (OGD), HFD-600 (Hare), HFD-658 (R.M.Mhatre, A.P.Patel), Drug File, Division File.